IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT	: Laurence A. Cole
U.S. APPLICATION NO.	: 10/616,323
FILING DATE	: July 9, 2003
TITLE	: Hyperglycosylated hCG (Invasive Trophoblast Antigen) In Differential Diagnosis of Malignant or Invasive Trophoblast Disease
GROUP ART UNIT	: 1642
EXAMINER	: Peter J. Reddig

Commissioner for Patents
Mailstop Amendment
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF DR. LAURENCE A. COLE

I, Dr. Laurence A. Cole, declare as follows:

1. I am a citizen of the United States of America.

2. In 1982, I received a Ph.D. in biochemistry from the Medical College of Wisconsin, Milwaukee, Wisconsin.

3. From February, 1982 to October 1983, I was a Postdoctoral Research Fellow in the Department of Pharmacology, University of Michigan, Ann Arbor, Michigan.

4. From October, 1983 to March, 1986 I was an Assistant Research Scientist in Internal Medicine and in the Reproductive Encrinology Program.

5. From March, 1986 to May, 1992, I was Assistant Professor in the Department of Obstetrics & Gynecology, Yale University, New Haven, Connecticut.

6. From May 1993 to October 1999, I was Associate Professor in the Department of Obstetrics & Gynecology, Yale University, New Haven, Connecticut.

7. Since November, 1999, I have been a Professor of Obstetrics & Gynecology and Biochemistry & Molecular Biology 1993 to October, 1999 at the University of New Mexico, Albuquerque, New Mexico. During this same period at the University of New Mexico, I have been the Chief of the Division of Women's Health Research.

8. Since November, 1999, I have been affiliate Professor In Obstetrics & Gynecology, Yale University, New Haven, Connecticut.

9. Since August, 2005, I have been the Privately Endowed "The Howard and Friedman Distinguished Professor of Obstetrics and Gynecology" at the University of New Mexico, Albuquerque, New Mexico.

10. I am inventor or co-inventor on several issued United States patents and have filed a number of patent applications which are presently pending, including the present patent application. The vast majority of these patents/patent applications relate to my expertise in determining the existence and outcome of pregnancy.

11. I am the recipient of a number of research, speaking and teaching awards in my area of expertise, as well as a member of a number of professional societies.

12. I presently have several active grants in the areas of pregnancy tests and pregnancy outcome.

13. I am the author or co-author of more than 150 peer-reviewed papers in the areas of pregnancy, pregnancy testing and pregnancy outcome.

14. I am the sole inventor of the present application which is directed to the following generic inventions:

a) a method for detecting the presence or absence of invasive trophoblast cells in a patient at risk for gestational trophoblastic disease or having a germ cell tumor as set forth in

pending claims 1, 2, 5, 7-11 and 46, and

b) a method for diagnosing quiescent gestational trophoblastic disease in a patient previously diagnosed as having quiescent gestational trophoblastic disease or previously treated for a gestational trophoblastic diseasethe highly accurate detection of pregnancy as set forth in pending claims 12- 16 and 47.

15. The crux of the inventions of the present inventions as claimed resides in the fact that one can measure the total amount of human chorionic gonadotropin hormone (hCG) in a sample from a patient as claimed, measure the amount of ITA (hyperglycosylated hCG) in the sample, determine the percentage of ITA compared to total hCG as indicated in the claims and if the percentage of ITA is above or below a predetermined percentage, as claimed, a diagnosis of the existence or absence of a disease state or condition may be made as claimed

15. I am familiar the above-referenced patent application, and have read the Examiner's office action dated October 5, 2009, and the patent references cited therein, as well as the Examiner's rejection of the pending claims as being non-enabled. I understand from this rejection that the Examiner contends that at the time of the filing of the present application, he believes that in order to determine the total amount of hCG in a sample as claimed, a person of ordinary skill would have to engage in undue experimentation in order to make the claimed measurements. I respectfully disagree.

16. It is my opinion and experience that measuring total hCG (i.e., intact hCG, ITA and optionally, β subunit hCG in a sample as is set forth in the pending claims at the time of the filing of the patent application in July, 2003 did not require undue experimentation. At that time, there were at least four available assays which could be used to make such a measurement and notwithstanding the availability of those ready-made assays, it was certainly within the skill of the ordinary practitioner to be able to make such an assay without undue experimentation.

17. In particular, at the time of the filing of the present application in July 2003, one of ordinary skill could use any of the following four assays to measure total hCG as claimed to provide a measure of predictive accuracy: DPC Immulite hCG test (DPC Biermann, Germany), US (RIA) of Yale University, Roche Elecsys and Siemens (Dade) Stratus, among others. In addition, development of an assay which could measure intact hCG and ITA and optionally β submit hCG was something that could be done with a degree of success, as evidenced by the number of

conforming assays which were present at the time of the filing of the present application.

18. In addition to the above-described assays, and the assays which are set forth in the present application on pages 7-10, it is my opinion that it is possible to provide numerous additional assays to measure total hCG and ITA in order to practice the present invention without requiring that the practitioner engage in undue experimentation. I understand that the term "undue experimentation" means that although some amount of routine experimentation will be required by a competent lab technician to make an assay work or to otherwise measure total hCG and ITA in a sample, that the amount of experimentation required will not be undue or extraordinary. Based upon the foregoing, I believe that there are numerous ways of measuring total hCG as set forth in the claims which can be competently and routinely performed by a person of ordinary skill and that a determination of total hCG and ITA as claimed and the percentage of ITA of total hCG in the sample is indicative of a determination of the presence or absence of a disease state or condition as claimed.

19. I understand that the Examiner also contends that monoclonal antibody B152 can not be used to measure total ITA or hyperglycosylated hCG in a sample. I respectfully disagree with the Examiner's characterization inasmuch as monoclonal antibody B152 is and has been shown to be selective for binding ITA in a sample as claimed and can be used to measure total ITA in a sample based upon that selectivity. I believe that the use of monoclonal antibody B152 to measure total ITA in a sample is straight forward and requires little, if any experimentation. Such a measurement is simple and accurate and readily applied to my invention.

20. I also understand that the Examiner has rejected the claims of the present application based upon the teachings in the reference, Khanlian, et al., *American J. of Obsterics and Gynecology,* May, 2003 188:1254-9 ("Khanlian, et al."). This is a reference which relates to the present invention and which was published less than two months before the filing date of the present application.

21. Ms. Sarah A. Khanlian is the first named author on the above-identified reference, Harriet O. Smith, M.D. is the second named author and I am the third named author on that publication.

22. With reference to Khanlian, et al., Ms. Khanlian at all times was a technician in

my laboratory who conducted experiments as described in that reference under my supervision, direction and control. Dr. Harriet Smith was a clinician who provided samples from a number of patients to be used in the studies which are described in the reference.

23. I originated the hypothesis and experimental design of the experiments which gave rise to the Khanlian, et al. paper. I also drew the conclusions from the data which were obtained from the experiments. Ms. Khanlian, who conducted those experiments under my direction, supervision and control was named as a co-author of the Khanlian, et al., paper because of her competent laboratory/technical work in performing the hands-on experiments. Dr. Smith, a clinician who provided samples from the clinic from patients in order to test those samples, was named as a co-author of the Khanlian, et al. paper because of the valuable contributions she made in obtaining and providing the clinical samples from patients to be tested pursuant to the experiments which were conducted by Ms. Khanlian.

24. I further declare that all statements made herein of my own personal knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: January 4, 2010

Laurence A. Cole, Ph.D.